

We claim

1. An angiogenesis inhibitory composition comprising an angiogenesis inhibiting compound and an antiinflammatory drug.

2. The angiogenesis inhibitory composition of Claim 1 wherein the antiinflammatory drug is a steroid.

3. The angiogenesis inhibitory composition of Claim 2 wherein the steroid is selected from the group consisting of cortisol, corticosterone, hydrocortisone, hydrocortisol, cortisone, prednisone, prednisolone, dexamethasone, beclomethasone, betamethasone, mometasone, mometasone furoate, budesonide, triamcinolone acetonide, and fluticasone.

4. The angiogenesis inhibitory composition of Claim 1 wherein the antiinflammatory drug is a nonsteroidal, antiinflammatory drug (NSAID).

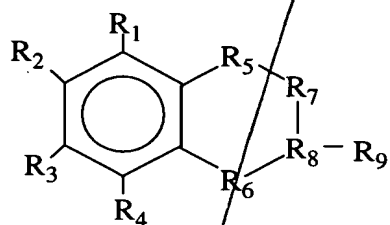
5. The angiogenesis inhibitory composition of Claim 4 wherein the NSAID is selected from group consisting of aspirin, acetaminophen, ibuprofen, esculetin, phenidone, quercetin, ketoprofen, nordihydroguaiaretic acid (NDGA), sulindac, sulindac sulfone, sulindac sulfide, indomethacin, NS-398 (a cyclooxygenase-2 inhibitor), cyclooxygenase-1 inhibitors, methylheptyl imidazole, furegrelate sodium, SKF525AHCL, thromboxane inhibitors, toradol, ecasa, salsalate, diflunisal, mefenamic acid, naproxen, naproxen sodium, floctafenine, meclofenamate, phenylbutazone, oxyphenbutazone, diclofenac, etodolac, fenoprofen, flufenamic acid, flurbiprofen, piroprofen, tolmetin, apazone, fenbufen, nabumetone, oxaprozin, piroxicam, salicylate, and tenoxicam.

6. The angiogenesis inhibitory composition of Claim 5 wherein the NSAID is selected from indomethacin and sulindac.

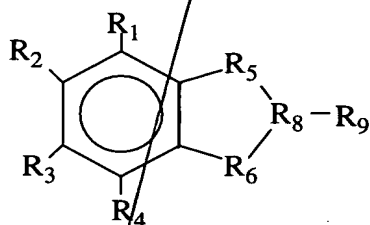
7. The angiogenesis inhibitory composition of Claim 1 wherein the angiogenesis inhibiting compound is selected from the group consisting of

(1) a compound selected from the formula

A)

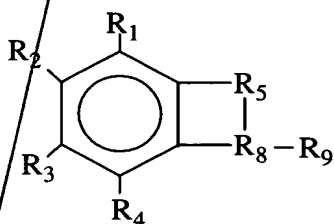


B)



or

C)

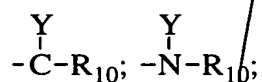


wherein

R₁ - R₄ are each independently selected from H; OH; =O; straight or branched chain alkanes, alkenes, and alkynes; cyclic alkanes, alkenes, and alkynes; combinations of cyclic and acyclic alkanes, alkenes, and alkynes; alcohol, aldehyde, ketone, carboxylic acid, ester, or ether moieties in combination with acyclic, cyclic, or combination acyclic/cyclic moieties; aza; amino; -XO_n or -O-

XO_n , where $\text{X}=\text{N}$ and $n=2$, $\text{X}=\text{S}$ and $n=2$ or 3 , or $\text{X}=\text{P}$ and $n=1-3$; and halogens;

$\text{R}_5 - \text{R}_8$ are each independently selected from



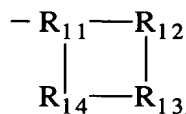
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or $-\text{O}-$, where Y is absent and R_{10} is $=\text{O}$ or Y and R_{10} are each independently the same as R_1 ;

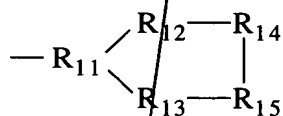
and R_9 is a moiety selected from the group consisting of

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D)

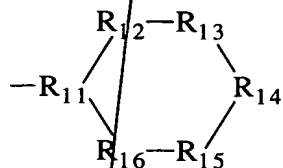


E)

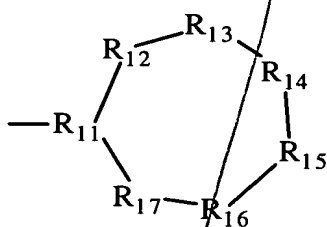


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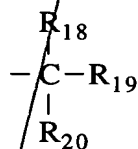
F)



G)



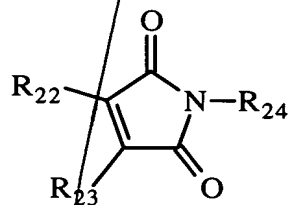
and H)



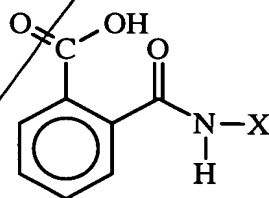
wherein each of R11 - R17 is independently the same as R5, and wherein R18, R19 and R20 are each independently selected from

H, CH₃, $\text{-}\overset{\text{O}}{\parallel}\text{C}\text{-OH}$, $\text{-}\overset{\text{O}}{\parallel}\text{C}\text{-NH}_2$, $\text{-(CH}_2\text{)}_n\text{-}\overset{\text{O}}{\parallel}\text{C}\text{-OH}$, and $\text{-(CH}_2\text{)}_n\text{-}\overset{\text{O}}{\parallel}\text{C}\text{-NH}_2$,
and n=1 through 4;

(2) a compound selected from the formula



where R22 and R23 are each independently H, F, Cl, Br, I, CH₃, or -CH₂-CH₃;
and R24 is H, CH₃, or -CH₂-CH₃;
and

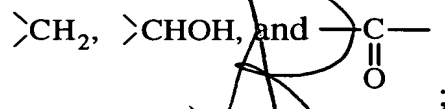
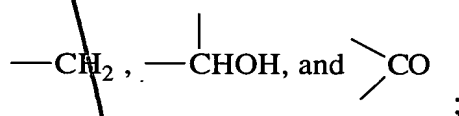
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The diagram shows a benzene ring with a central circle. Substituents are labeled R₁ through R₆ around the ring. R₁ is at the top, R₂ at top-left, R₃ at bottom-left, R₄ at the bottom, R₅ at top-right, and R₆ at bottom-right. A five-membered ring is fused to the right side of the benzene ring, sharing the bond between R₅ and R₆. This five-membered ring has vertices labeled R₅, R₆, R₈, and R₉, with an additional bond between R₈ and R₉.

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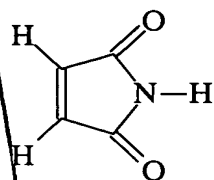


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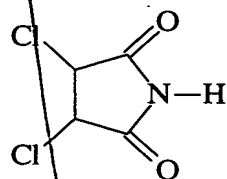
and R₁₅ is -O- or $\text{--}\overset{\text{R}_{21}}{\underset{|}{\text{N}}}\text{--}$, where R₂₁ is H, CH₃, or OH.

9. The angiogenesis inhibitory composition of claim 7 wherein the angiogenesis inhibiting compound is selected from the group consisting of

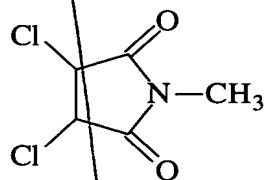
I)



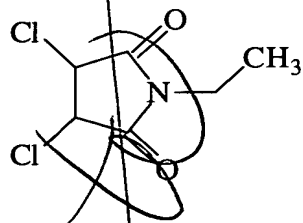
J)



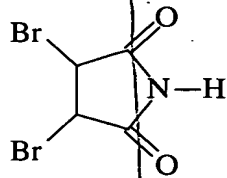
K)



L)



M)

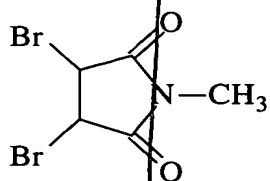


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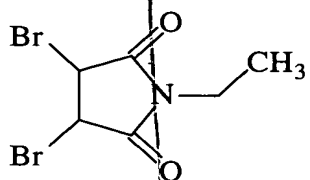
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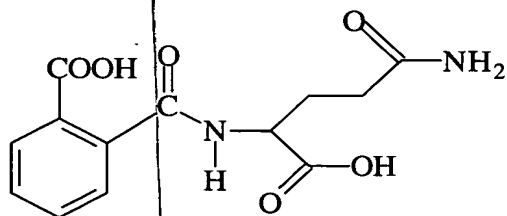
N)



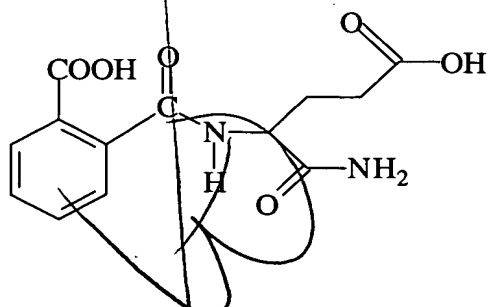
O)



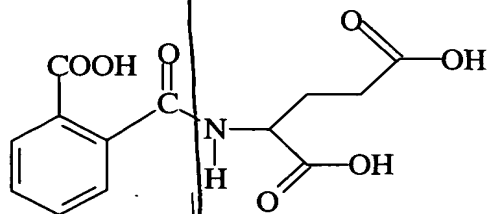
P)



Q)



R)



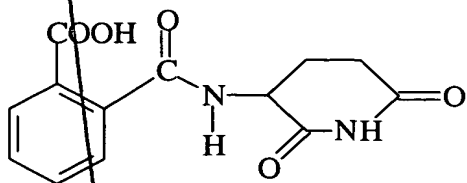
and

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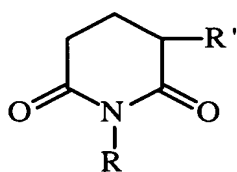
S)



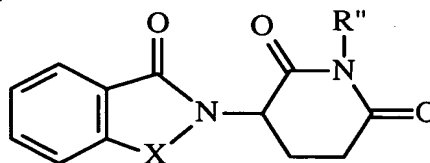
10. The angiogenesis inhibitory composition of Claim 7 wherein the angiogenesis inhibiting compound is selected from the group consisting of thalidomide, metabolites of thalidomide, thalidomide analogs, epoxides of thalidomide, hydolysis products thereof, EM-12, metabolites of EM-12, epoxides of EM-12, hydolysis products thereof, EM-138, metabolites of EM-138, epoxides of EM-138, hydolysis products thereof, N-phthaloyl-DL-glutamic acid (PGA), N-phthaloyl-DL-glutamine anhydride, and mixture thereof.

11. The angiogenesis inhibitory composition of Claim 10 wherein the inhibiting compound is selected from

(I)



(II)



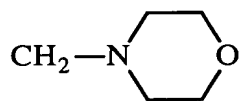
and

wherein R is selected from the group consisting of H, (C₁-C₆)alkyl, phenyl, and benzyl; and

R' is selected from the group consisting of phthalimido and succinimido;

wherein X is CH₂ or C=O; and

R" is H, -CH₂CH₃, -C₆H₅, -CH₂C₆H₅, -CH₂CH=CH₂, or

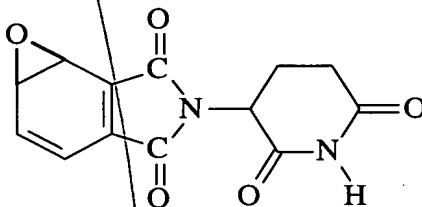


and

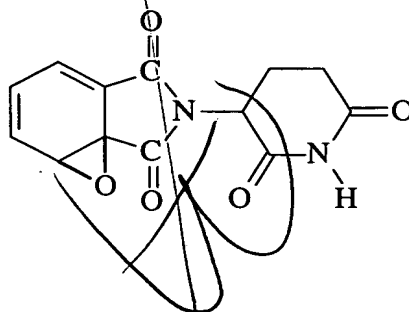
(III) hydrolysis products of (II) wherein R" is H and the piperidino ring or both the piperidino and the imido ring are hydrolyzed.

12. The angiogenesis inhibitory composition of Claim 10 wherein the angiogenesis inhibiting compound is selected from the group consisting of

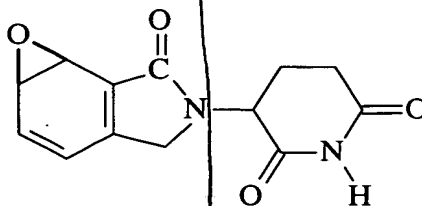
III)



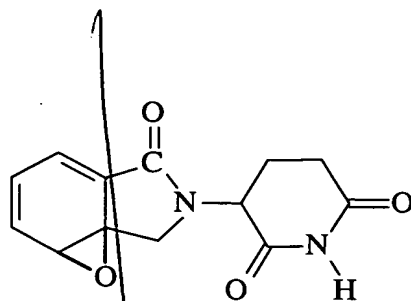
IV)



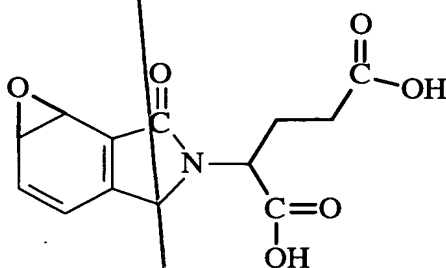
V)



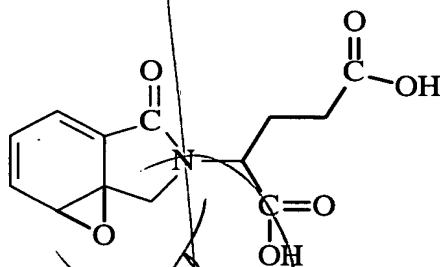
VI)



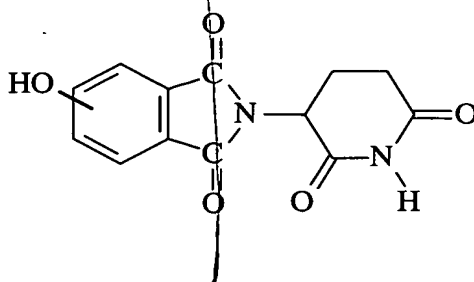
VII)



VIII)

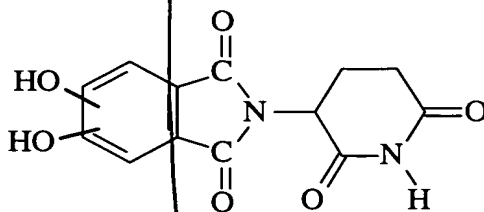


IX)

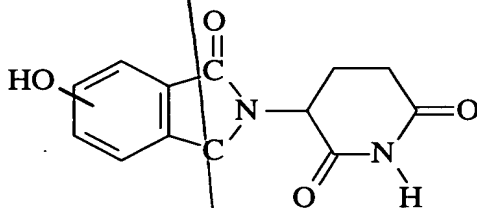


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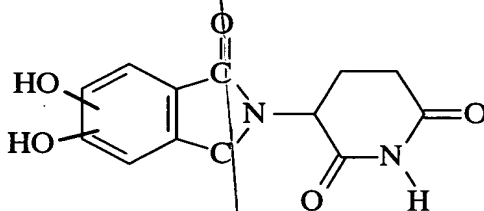
X)



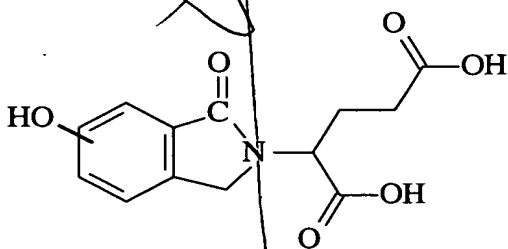
XI)



XII)



XIII)



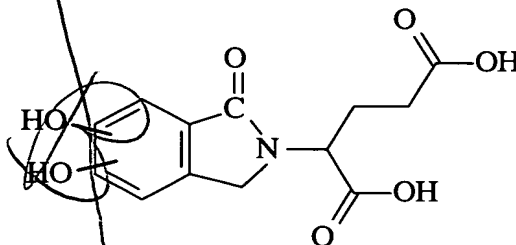
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XIV)



5 13. A method for inhibiting angiogenesis in a human or animal comprising administering to the human or animal a composition comprising a nonsteroidal, antiinflammatory drug (NSAID).

*Sub
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10 14. The method of Claim 13 wherein the composition further comprises an angiogenesis inhibiting compound.

15 15. A method for inhibiting angiogenesis in a human or animal comprising administering to the human or animal a composition comprising an angiogenesis inhibiting compound and an antiinflammatory compound.

*Sub
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B5*
16. A method for treating an angiogenesis dependent disease in a human or animal having such a disease comprising administering to the human or animal a composition comprising a nonsteroidal, antiinflammatory drug (NSAID).

17. The method of Claim 16 wherein the composition further comprises an angiogenesis inhibiting compound.

*Sub
B6*
25 18. The method of Claim 16 wherein the angiogenesis dependent disease is selected from the group consisting of macular degeneration, diabetic retinopathy, neovascular glaucoma, retrolental fibroplasia, proliferative vitreoretinopathy, solid tumors, blood-borne tumors, leukemia, hemangioma, psoriasis, Kaposi's sarcoma, Crohn's
30 disease, ulcerative colitis, cancer, retinopathy of prematurity, corneal

5 graft rejection, epidemic keratoconjunctivitis, Vitamin A deficiency,
contact lens overwear, atopic keratitis, superior limbic keratitis,
pterygium keratitis sicca, sjogren's syndrome, acne rosacea,
phlyctenulosis, syphilis, *Mycobacteria* infections, lipid degeneration ,
10 chemical burns, bacterial ulcers, fungal ulcers, *Herpes simplex*
infections, *Herpes zoster* infections, Mooren's ulcer, Terrien's marginal
degeneration, marginal keratolysis, trauma, rheumatoid arthritis,
systemic lupus, polyarteritis, Wegener's sarcoidosis, scleritis, Stevens-
Johnson disease, radial keratotomy, corneal graft rejection, sickle cell
15 anemia, pseudoxanthoma elasticum, pemphigoid, Paget's disease, vein
occlusion, artery occlusion, carotid obstructive disease, chronic uveitis,
chronic vitritis, Lyme's disease, systemic lupus erythematosus, Eales'
disease, Behcet's disease, presumed ocular histoplasmosis, Best's disease,
myopia, optic pits, Stargardt's disease, pars planitis, chronic retinal
20 detachment, hyperviscosity syndromes, toxoplasmosis, post-laser
complications, and rubeosis.

25 19. A method for treating an angiogenesis dependent
disease in a human or animal having such a disease comprising
administering to the human or animal a composition comprising an
angiogenesis inhibiting compound and an antiinflammatory compound.

30 20. The method of Claim 19 wherein the angiogenesis
dependent disease is selected from the group consisting of macular
degeneration, diabetic retinopathy, neovascular glaucoma, retrolental
fibroplasia, proliferative vitreoretinopathy, solid tumors, blood-borne
tumors, leukemia, hemangioma, psoriasis, Kaposi's sarcoma, Crohn's
disease, ulcerative colitis, cancer, retinopathy of prematurity, corneal
35 graft rejection, epidemic keratoconjunctivitis, Vitamin A deficiency,
contact lens overwear, atopic keratitis, superior limbic keratitis,
pterygium keratitis sicca, sjogren's syndrome, acne rosacea,
phlyctenulosis, syphilis, *Mycobacteria* infections, lipid degeneration ,
chemical burns, bacterial ulcers, fungal ulcers, *Herpes simplex*
infections, *Herpes zoster* infections, Mooren's ulcer, Terrien's marginal
degeneration, marginal keratolysis, trauma, rheumatoid arthritis,

systemic lupus, polyarteritis, Wegener's sarcoidosis, scleritis, Stevens-Johnson disease, radial keratotomy, corneal graft rejection, sickle cell anemia, pseudoxanthoma elasticum, pemphigoid, Paget's disease, vein occlusion, artery occlusion, carotid obstructive disease, chronic uveitis, chronic vitritis, Lyme's disease, systemic lupus erythematosus, Eales' disease, Behcet's disease, presumed ocular histoplasmosis, Best's disease, myopia, optic pits, Stargardt's disease, pars planitis, chronic retinal detachment, hyperviscosity syndromes, toxoplasmosis, post-laser complications, and rubeosis.

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add B3

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